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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF	:
AGATHE SUBTIL, ET AL.	: EXAMINER: FORD, V.
SERIAL NO: 10/014,670	:
FILED: DECEMBER 14, 2001	: GROUP ART UNIT: 1645
FOR: SECRETED CHLAMYDIA POLYPEPTIDES AND METHOD FOR IDENTIFYING SUCH POLYPEPTIDES BY THEIR SECRETION BY A TYPE III SECRETION PATHWAY OF A GRAM NEGATIVE BACTERIA	:

APPEAL BRIEF

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313
SIR:

This brief is submitted in response to the final rejection dated February 1, 2007.

REAL PARTY OF INTEREST

The real parties of interest herein are Institut Pasteur, Centre National de la Recherche Scientifique, and INSERM, all of Paris, France.

RELATED APPEALS AND INTERFERENCES

To the best of Appellants' knowledge, there are no other appeals or interferences which will directly affect or be directly affected by, or have a bearing on, the Board's decision in this appeal.

STATUS OF CLAIMS

Claims 7-10 and 30-47 are active in this application. Claims 30-33 and 38-43 are withdrawn to a Restriction Requirement imposed by the Office. Claims 7-10, 34-37 and 44-47 are currently rejected. The pending, examined and rejected claims are reproduced in Appendix I. Withdrawn claims are not reproduced.

STATUS OF AMENDMENTS

There are no outstanding amendments in this case.

SUMMARY OF CLAIMED SUBJECT MATTER

Independent Claims 7 and 8 are reproduced below with brackets indicating page and line number for corresponding discussion in the specification.

7. A method for identifying a secreted *Chlamydia* polypeptide wherein said method comprises (a) providing a recombinant expression vector containing at least DNA coding for the polypeptide of interest; (b) transforming a Gram-negative strain containing a type III secretion pathway **[PAGE 14, LAST PARAGRAPH]** with said recombinant vector; (c) expressing said vector in said Gram-negative transformed strain; and (d) detecting the secretion of said DNA expression product; wherein the secretion of said expression product indicates that it corresponds to a secreted *Chlamydia* polypeptide. **[PAGE 10, 1ST PARAGRAPH]**

8. (Original) A method for identifying a secreted *Chlamydia* polypeptide wherein said method comprises (a) providing a recombinant expression vector containing at least DNA coding for the polypeptide of interest fused to a reporter gene; (b) transforming a Gram-negative strain containing a type III secretion pathway **[PAGE 14, LAST PARAGRAPH]** with said recombinant vector; (c) expressing this vector in said transformed Gram-negative strain; and (d) detecting the secretion of said reporter gene expression product; wherein the secretion of said expression product indicates that the fused DNA contains at least a polynucleotide corresponding to a secreted *Chlamydia* polypeptide. **[PAGE 10, 2ND PARAGRAPH]**

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. The first rejection to be reviewed on appeal is of Claims 7-10, 34-37 and 44-47 under 35 U.S.C. § 103(a) in view of Demers (WO 9958714), Graffais (U.S. patent no. 6,559,294) and Kalman (*Nature Genetics*, vol. 21, April 1999).
2. The second rejection to be reviewed on appeal is of Claims 7-10, 34-37 and 44-47 under 35 U.S.C. § 103(a) over Stephens (U.S. patent no. 6,822,071) in view of Demers (WO 9958714).

ARGUMENT

In rejecting a claim under 35 U.S.C. § 103(a), the USPTO must support its rejection by "substantial evidence" within the record,[1] and by "clear and particular" evidence[2] of a suggestion, teaching, or motivation to combine the teachings of different references. As discussed above, there is no substantial evidence, nor clear and particular evidence, within the record that teaches all of the limitations of the pending claims. Without such suggestion or teaching and absent improper hindsight reconstruction,[3] the pending claims are believed to be non-obvious and patentable over the applied references.

Chlamydia bacteria, which are gram negative bacteria, are human pathogens causing a number of diseases (see page 1 of the specification). Part of the pathogenesis of Chlamydia involves the expression and secretion of a number of proteins (see pages 2-4 of the specification). Generally, protein secretion in gram negative bacteria, involves at least four different pathways (page 5, 1st full paragraph of the specification). As discussed in the paragraph bridging pages 5-6 of the specification, since there are no genetic tools to manipulate and study Chlamydia gene expression and protein secretion, another way to analyze Chlamydia gene expression and pathogenesis.

In view of this background, "the inventors have shown that several chlamydial proteins, including members of the Inc family and proteins selected for a hydropathic profile similar to that of Inc proteins, are secreted by the type II secretion machinery of *S. flexneri*." (*S. flexneri* is a Shigella specie). Thus, to better understand the pathogenesis of the

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[1] In re Gartside, 203 F3d 1305, 53 USPQ2d 1769 (Fed. Cir. 2000) (holding that, consistent with the Administrative Procedure Act at 5 USC 706(e), the CAFC reviews the Board's decisions based on factfindings, such as 35 U.S.C. § 103(a) rejections, using the 'substantial evidence' standard because these decisions are confined to the factual record compiled by the Board.)

[2] In re Dembiczak, 175 F3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999) ("We have noted that evidence of a suggestion, teaching, or motivation to combine may flow from the prior art references themselves, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved, although 'the suggestion more often comes from the teachings of the pertinent references.' The range of sources available, however, does not diminish the requirement for actual evidence. That is, the showing must be clear and particular.") (emphasis added).

[3] See MPEP 2141, stating, as one of the tenets of patent law applying to 35 USC 103, that "[t]he references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention."

Chlamydia bacteria and to develop ways to better diagnose infection and devise treatments, the present inventors have discovered that Chlamydia proteins can be expressed and detected in gram negative bacterial cell resulting in the claimed invention relating to a method for identifying a secreted *Chlamydia* polypeptide by causing expression of a polypeptide of interest in a Gram-negative strain containing a type III secretion pathway and subsequently determining whether the protein is secreted.

The United States Supreme Court in *KSR Intern. Co. v. Teleflex, Inc.*, 127 S.Ct. 1727 (2007) stated that

> when a patent claims a structure already known in the prior art that is altered by the mere substitution of one element for another known in the field, the combination must do more than yield a predictable result.

Id. at 1740.

In the present situation, the art cited by the Examiner does not provide the requisite predicable result because the art teaches different methods with a lack of expectation that the claimed invention would work as demonstrated by the work presented in the present application.

Rejection 1 based on Graffais, Demers and Kalman

The claimed invention is to an entirely different method of identifying secreted *Chlamydia* proteins compared to what is described or suggested by the combination of cited art. Specifically, Demers describes screening for agent/compounds that **change the expression** of type III secretory proteins and/or which **block secretion** through this pathway. Specifically, pages 1, lines 8-9, page 2, lines 14-16 and page 3, lines 1-2 of Demers:

> The invention also provides methods of identifying molecules that are able to activate or inhibit secretion in wild-type strains of gram-negative bacteria. Page 3, lines 1-2 of Demers

Graffais describes a number of Chlamydia proteins some of which are characterized as Type II secreted proteins (see, e.g., col. 22, lines 62-67). The Office cites column 40 of Graffais for a teaching of expressing proteins and detecting them using any known technique (see Advisory Action at page 3). However, Graffais' teachings are not focused on this but rather disclose the genes and then go on to describe that the genes and their corresponding proteins could be used for almost any imaginable use of such molecules, e.g., hybridization, eliciting an immune response, identifying compounds which block pathogenesis and others (see col. 43, lines 1-13; col. 50, lines 4-16), col. 59, line 57 to col. 60, line 16; col. 60, lines 46-56; col. 61, lines 21-33 and col. 63, lines 1-8).

Kalman is cited merely for the proposition that certain Chlamydia genes were known (see page 4 of the final Office Action and page 3 of the Advisory Action) but does not add anything relating to the method as claimed.

The Office's rationale for maintaining the rejection lacks merit for two reasons.

First, one would not have used Demers secretion system as alleged by the Office because doing so would be contrary to what is taught (*KSR* does not modify the notion that if art teaches NOT to do something then obviousness still exists; see also MPEP § 2141.02

(prior art must be considered in its entirety, including disclosures that teach away from the claims)). Specifically, Demers entire disclosure is directed to looking for agents that block secretion or change expression patterns NOT for determining whether a certain Chlamydia protein is one that can be secreted through the type III pathway.

Second, the cited art provides no reason to believe that the expression of Chlamydia proteins would, in fact, work in other gram negative strains such as Shigella. No evidence as to why the Office concludes that genes from such different organisms would be expressed nor would be properly secreted by the Type III machinery of that cell. The Office simply makes a conclusion without supporting facts. The Office should take note that as a prelude to the Inventors description that they have discovered that certain Chlamydia proteins could be expressed and secreted in Shigella, the Inventors state that another prior art publication in *Molecular Microbiology* describes expression of other proteins in Shigella, there are phylogenic differences between Chlamydia from other organisms (see page 7 of the specification) and therefore it is implied that no *a priori* conclusion could be drawn as to the success of expression of Chlamydia proteins in other bacterial cells, such as Shigella. (*KSR, supra*).

Moreover, heterologous secretion of a secreted Chlamydia polypeptide can be obtained only if the signal of the Chlamydia polypeptide is identical to the signal of the bacteria in which the secretion is tested. This was not obvious for Shigella first because the signal is still unknown and second because of the phylogenic distance of Chlamydia with the other organisms (see paragraph 10 of the specification). One could have thought that the signals had become different during evolution. This is particularly strengthen by the fact that it is known that the proteins which make the Chlamydia secretion machinery are not well conserved compared to the protein which make the secretion machinery of bacteria as Yersinia, Salmonella, Pseudomonas etc. which could also have been used as models.

In addition, many secreted proteins need to be expressed together with a chaperone protein. Examples in the literature for the necessity of coexpressing a chaperone protein to get secretion in Salmonella are listed below (Previously submitted into the record on November 6, 2006):

Parsot et al Curr Opin Microbiol. 2003 Feb;6(1):7-14

Tuckerdagger and Galan, J Bacteriol. 2000 Apr;182(8):2262-8

For the presence of functional chaperone proteins in Chlamydia, see below (Abstracts attached):

Fields et al J Bacteriol. 2005 Sep;187(18):6466-78

Slepenkin et al J Bacteriol. 2005 Jan;187(2):473-9

And again, Demers does not describe the use of their system as a screening method for discovering new secreted proteins, but only as a screening method for finding inhibitors/activators of secretion.

In view of the above, the combination of Demers, Graffais and Kalman fail to describe a method for identifying a secreted *Chlamydia* polypeptide including the steps as set forth in independent Claims 7 and 8. As the combination of cited publications fail to describe or suggest each and every limitation of the claimed invention, withdrawal of the rejection under 35 U.S.C. § 103(a) is requested.

Rejection 2 based on Stephens and Demers

To the newly raised rejection, it should be recognized that the Stephens patent describes the identification of chlamydia polypeptides and also that these polypeptides can be expressed from cells transformed with the corresponding nucleic acids using conventional cell lines such as *E. coli* (see columns 15-16).

The Examiner acknowledges that the Stephens patent does not describe the expression of chlamydia polypeptides in gram-negative bacterial strains containing a type III secretion pathway but for this the Examiner relies again on the Demers disclosure. On this basis, the Examiner alleges that one would have expressed the proteins in Stephens using the bacteria strains described in Demers. (see discussion on pages 5-6 of the Official Action).

Applicants disagree.

Neither of Stephens nor Demers describes a method for identifying secreted proteins but rather the general methodology for expressing proteins (which is even acknowledged by Stephens in column 15). It must be understood that expression of a protein and secretion of the same are not necessarily the same thing, e.g., a protein can be expressed without also being secreted.

Again, Demers describes screening for agent/compounds that **change the expression** of type III secretory proteins and/or which **block secretion** through this pathway (see pages 1, lines 8-9, page 2, lines 14-16 and page 3, lines 1-2 of Demers). Therefore, Demers combined with Stephens simply fails to teach and/or suggest the claimed invention.

Moreover, heterologous secretion of a secreted Chlamydia polypeptide can be obtained only if the signal of the Chlamydia polypeptide is identical to the signal of the bacteria in which the secretion is tested. This was not obvious for Shigella first because the

signal is still unknown and second because of the phylogenic distance of Chlamydia with the other organisms (see paragraph 10 of the specification). One could have thought that the signals had become different during evolution. This is particularly strengthen by the fact that it is known that the proteins which make the Chlamydia secretion machinery are not well conserved compared to the protein which make the secretion machinery of bacteria as Yersinia, Salmonella, Pseudomonas etc. which could also have been used as models. *(KSR, supra)*.

And again, Demers does not describe the use of their system as a screening method for discovering new secreted proteins, but only as a screening method for finding inhibitors/activators of secretion.

Accordingly, withdrawal of the rejection based on Stephens and Demers is requested.

The above comments apply in equal force to each pending claim. The dependent claims all contain further limitations that establish their patentability apart from those in independent Claims 7 and 8.

CONCLUSION

Accordingly, in view of the above remarks and reasons explaining the patentable distinctness of the presently appealed claims over the applied prior art, Appellants request reversal of the final rejection.

Respectfully submitted,

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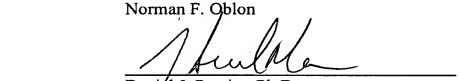

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Appendix 1 (Claims)

Claims 1-6 (Cancelled).

7. (Original) A method for identifying a secreted *Chlamydia* polypeptide wherein said method comprises (a) providing a recombinant expression vector containing at least DNA coding for the polypeptide of interest; (b) transforming a Gram-negative strain containing a type III secretion pathway with said recombinant vector; (c) expressing said vector in said Gram-negative transformed strain; and (d) detecting the secretion of said DNA expression product; wherein the secretion of said expression product indicates that it corresponds to a secreted *Chlamydia* polypeptide.

8. (Original) A method for identifying a secreted *Chlamydia* polypeptide wherein said method comprises (a) providing a recombinant expression vector containing at least DNA coding for the polypeptide of interest fused to a reporter gene; (b) transforming a Gram-negative strain containing a type III secretion pathway with said recombinant vector; (c) expressing this vector in said transformed Gram-negative strain; and (d) detecting the secretion of said reporter gene expression product; wherein the secretion of said expression product indicates that the fused DNA contains at least a polynucleotide corresponding to a secreted *Chlamydia* polypeptide.

9. (Original) A method according to Claims 7 or 8 wherein said Gram-negative strain containing a type III secretion pathway is a *Shigella* strain.

10. (Original) A method according to Claims 7 or 8 wherein said expression product is secreted by a type III secretion pathway.

34. (Previously Presented) The method according to Claim 7, wherein said secreted polypeptide is selected from the group consisting of IncA, IncB, IncC, CPn0026, CPn0067, CPn0130, CPn0146, CPn0174, CPn0186, CPn0211, CPn0243, CPn0277, CPn0284, CPn0292, CPn0357, CPn0365, Cpn1027, CPn0028, CPn0049, CPn0066, CPn0132,

CPn0220, CPn0223, CPn0226, CPn0267, CPn0648, Cpn0829, CPn0009, CPn0012, CPn0063, CPn0167, CPn0175, CPn0181, CPn0105, CPn0287, CPn0330, CPn0334, CPn0374, CPn0379, CPn0705, CPn0710, CPn0711, CPn0820, Cpn0821, CPn1016, and CPn1022.

35. (Previously Presented) The method according to Claim 8, wherein said secreted polypeptide is selected from the group consisting of IncA, IncB, IncC, CPn0026, CPn0067, CPn0130, CPn0146, CPn0174, CPn0186, CPn0211, CPn0243, CPn0277, CPn0284, CPn0292, CPn0357, CPn0365, Cpn1027, CPn0028, CPn0049, CPn0066, CPn0132, CPn0220, CPn0223, CPn0226, CPn0267, CPn0648, Cpn0829, CPn0009, CPn0012, CPn0063, CPn0167, CPn0175, CPn0181, CPn0105, CPn0287, CPn0330, CPn0334, CPn0374, CPn0379, CPn0705, CPn0710, CPn0711, CPn0820, Cpn0821, CPn1016, and CPn1022.

36. (Previously Presented) The method according to Claim 9, wherein said secreted polypeptide is selected from the group consisting of IncA, IncB, IncC, CPn0026, CPn0067, CPn0130, CPn0146, CPn0174, CPn0186, CPn0211, CPn0243, CPn0277, CPn0284, CPn0292, CPn0357, CPn0365, Cpn1027, CPn0028, CPn0049, CPn0066, CPn0132, CPn0220, CPn0223, CPn0226, CPn0267, CPn0648, Cpn0829, CPn0009, CPn0012, CPn0063, CPn0167, CPn0175, CPn0181, CPn0105, CPn0287, CPn0330, CPn0334, CPn0374, CPn0379, CPn0705, CPn0710, CPn0711, CPn0820, Cpn0821, CPn1016, and CPn1022.

37. (Previously Presented) The method according to Claim 10, wherein said secreted polypeptide is selected from the group consisting of IncA, IncB, IncC, CPn0026, CPn0067, CPn0130, CPn0146, CPn0174, CPn0186, CPn0211, CPn0243, CPn0277, CPn0284, CPn0292, CPn0357, CPn0365, Cpn1027, CPn0028, CPn0049, CPn0066, CPn0132, CPn0220, CPn0223, CPn0226, CPn0267, CPn0648, Cpn0829, CPn0009, CPn0012,

CPn0063, CPn0167, CPn0175, CPn0181, CPn0105, CPn0287, CPn0330, CPn0334, CPn0374, CPn0379, CPn0705, CPn0710, CPn0711, CPn0820, Cpn0821, CPn1016, and CPn1022.

44. (Previously Presented) The method according to claim 7, wherein said secreted *Chlamydia* polypeptide is a *Chlamydia pneumoniae* polypeptide.

45. (Previously Presented) The method according to claim 8, wherein said secreted *Chlamydia* polypeptide is a *Chlamydia pneumoniae* polypeptide.

46. (Previously Presented) The method according to claim 7, wherein said secreted *Chlamydia* polypeptide is a *Chlamydia trachomatis* polypeptide.

47. (Previously Presented) The method according to claim 8, wherein said secreted *Chlamydia* polypeptide is a *Chlamydia trachomatis* polypeptide.

APPENDIX II (EVIDENCE)

Entered in the record on November 6, 3006

Parsot et al Curr Opin Microbiol. 2003 Feb;6(1):7-14

-Tuckerdagger and Galan, J Bacteriol. 2000 Apr;182(8):2262-8

-Fields et al J Bacteriol. 2005 Sep;187(18):6466-78

-Slepenkin et al J Bacteriol. 2005 Jan;187(2):473-9

RELATED PROCEEDINGS APPENDIX

None.